Physician's Prescribing Information

EPIRUBICIN INOVAMED

Epirubicin Hydrochloride 2 mg/ml Solution for Injection

The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health

TRADE NAME OF MEDICINAL PRODUCT: EPIRUBICIN INOVAMED

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each milliliter of solution for injection contains 2 mg epirubicin hydrochloride.

The content of sodium is 3.54 mg per ml and per vial is as follows:
5 ml vial 17.71 mg, 10 ml vial 35.42 mg, 25 ml vial 88.55 mg, 50 ml vial 177.1 mg and 100 ml vial 354.2 mg.
For a full list of excipients, see section "**List of excipients** "

PHARMACEUTICAL FORM: Solution for Injection. A clear red solution.

CLINICAL PARTICULARS
Therapeutic indications: For the treatment of wide spectrum of neoplastic diseases including breast carcinoma, lung carcinoma high doses, ovarian carcinoma, gastric carcinomas, soft tissue sarcoma. Intravesical administration of epirubicin has been found to be beneficial in the treatment of superficial bladder carcinomas and in the prophylaxis of recurrences after transurethral resection. I.V. administration for the treatment of advanced bladder carcinoma.

Posology and method of administration: Epirubicin is for intravenous or intravesical use only. The safety and efficacy of epirubicin in children has not been established. EPIRUBICIN INOVAMED solution for injection is compatible with both dextrose 5% and sodium chloride 0.9%.
Please refer to section "**Special precautions for disposal and other handling**" for instructions on the preparation and handling of the drug product.

Intravenous administration: It is advisable to administer epirubicin via the tubing of a free-running intravenous sodium chloride 0.9% infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see section "**Special warnings and precautions for use**"). In case of extravasation, administration should be stopped immediately.

Conventional dose: When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function.
If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose: Epirubicin as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:
- Lung cancer as a single agent – the recommended high starting dose of Epirubicin per cycle in adults (up to 135 mg/m^2) should be administered on day 1 or in divided doses on day s 1, 2 and 3, every 3 to 4 weeks. In combination therapy, the recommended high starting dose (up to 120 mg/m^2) should be administered on day 1, every 3 to 4 weeks.
- For high dose treatment, epirubicin may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

Breast Cancer: In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.
Lower doses (60-75 mg/m^2 for conventional treatment and 105-120 mg/m^2 for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

The following doses of epirubicin are commonly used in monotherapy and combination chemotherapy for various tumours, as shown:

	Epirubicin Dose (mg/m^2)[a]	
Cancer Indication	**Monotherapy**	**Combination Therapy**
Advanced ovarian cancer	60–90	50–100
Gastric cancer	60–90	50
SCLC	120	120
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	

[a] Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy: If epirubicin is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function: The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:
Serum Bilirubin: 24 - 51 μmol/l …… Dose Reduction: 50% ; Serum Bilirubin: > 51 μmol/l …… Dose Reduction: 75%

Impaired renal function: Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

Intravesical administration: Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see section "**Contraindications**"). Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:
8 weekly instillations of 50 mg/50 ml (diluted with sodium chloride 0.9%).
If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.
Carcinoma in situ of the bladder: Up to 80 mg/50 ml (depending on individual tolerability of the patient).
For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS:

Dose Epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent sterile sodium chloride 0.9%	Total volume for bladder installation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be retained intravesically for 1-2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

Contraindications: Epirubicin is contraindicated in:
- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to other antracyclines or anthracenediones.
- Persistent myelosuppression.
- Patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy.
- Patients treated with maximal cumulative doses of epirubicin and/or other anthracyclines (such as doxorubicin or daunorubicin) and anthracenediones.
- Patients with current or previous history of cardiac impairment (including New York Heart Association (NYHA) class IV heart failure, acute myocardial infarction and previous infarction with residual NYHA class III or class IV heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences).
- Unstable angina pectoris.
- Myocardiopathy.
- Patients with acute systemic infections
- Sever liver impairment
- Severe mucositis of the mouth, pharynx, oeasophagus, and gastro-intestinal tract.
- Lactation.

For intravesical administration, epirubicin is contraindicated in:
- Urinary tract infections
- Hematuria.
- Invasive tumours penetrating the bladder
- Catheterisation problems
- Vesical inflammation
- Large volume of residual urine
- Contracted bladder.

Special warnings and special precautions for use:
General: Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Patients should recover from acute toxicities (such as severe stomatitis or mucositis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.
While treatment with high doses of epirubicin (e.g., ≥ 90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m^2 every 3 to 4 weeks) the severity of the neutropenia and stomatitis / mucositis may be increased. Treatment with high doses of epirubicin does require special attention for possible clinical complications due to profound myelosuppression.
Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin.
Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin), (see section "**Posology and method of administration**").

Epirubicin may impart a red colour to the urine for one or two days after administration.

Cardiac Function: Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.
Early (i.e., acute) events: Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin treatment.
Late (i.e., delayed) events: Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug. Heart failure may appear several weeks after iscontinuing therapy with epirubicin and may be unresponsive to specific medical treatment.
In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly (see section "**Pharmacodynamic properties**"). An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment.
Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques. ECG changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or a specific method for following anthracycline-related cardiotoxicity.
The risk of serious cardiac impairment may be decreased through regular monitoring of the left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin with the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with ECG and MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.
Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin should be exceeded only with extreme caution.
Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section "**Interaction with other medicinal products and other forms of interaction**").
Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses (<900 mg/m^2) whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive. In the case of cardiac insufficiency the treatment with epirubicin should be discontinued.

Reproductive system: Epirubicin can have genotoxic effects. Therefore male patients treated with epirubicin are advised to use effective contraceptive methods and if appropriate and available, seek advise regarding conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.
Female patients should not become pregnant during treatment with epirubicin.
Men and women should use an effective method of contraception during treatment and for six months thereafter (see section "**Pregnancy and Lactation**").
Patients desiring to have children after completion of therapy should be advised to obtain genetic counseling if appropriate and available.

Effects at site of injection: Phlebosclerosis may result from injection into small vessels or repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site.

Extravasation: Extravasation of epirubicin from the vein during injection may cause local pain, severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.
Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately discontinued. The patient's pain may be relieved by cooling down the area and keeping it cool for 24 hours. The patient should be monitored closely during the subsequent period of time, as necrosis may occur several weeks after extravasation occurs. If necessary, a plastic surgeon should be consulted with a view to possible excision.

Hematologic toxicity: As with other cytotoxic agents, epirubicin may produce myelosuppression.During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug.Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the 10th and 14th day, values should return to normal by the 21st day; they are more severe with high dose schedules. Thrombocytopenia (< 100,000 platelets/mm^3) is experienced in very few patients, even following high doses of epirubicin. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary leukemia: Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.

Tumor-lysis syndrome: As with other cytotoxic agents, epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that this phenomenon may be recognised and properly managed. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumor-lysis syndrome.

Immunosuppressant effects/increased susceptibility to infections: Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin, may result in serious or fatal infections (see section "**Interaction with other medicinal products and other forms of interaction**").

Gastrointestinal: Epirubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver function: Epirubicin is mainly eliminated via the liver. Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (AST, SGT, alkaline phosphatase, serum total bilirubin). Patients with decreased liver function may experience slower clearance of drug with an increase in overall toxicity. For these patients a dose reduction is recommended (see section "**Posology and method of administration**" and "**Pharmacokinetic properties**"). Patients with severe hepatic impairment should not receive epirubicin (see section "**Contraindications**").

Renal function: Serum creatinine levels should be checked regularly prior to and during treatment. For patients with increased serum creatinine (>5 mg/dl) a dose reduction is proposed (see section "**Posology and method of administration**").

Other: As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of epirubicin.

Additional Warnings and Precautions for Other Routes of Administration:
Intravesical route: Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., uretheral obstruction due to massive intravesical tumors).

Intra-arterial route: Intra-arterial administration of epirubicin (transcatheter arterial embolization for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to druginduced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Interaction with other medicinal products and other forms of interaction: It is not recommended that EPIRUBICIN INOVAMED solution for injection be mixed with other medicinal products. However, epirubicin can be used in combination with other anti-cancer agents but patients should be monitored for additive toxicity, especially myelotoxicity and gastrointestinal toxicity.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon α_2b, paclitaxel and quinine. Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

Prior administration of higher doses (900 mg/m^2 and 1200 mg/m^2) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.

The co-administration of interferon α_2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.
One study has shown that paclitaxel clearance is reduced by epirubicin.
Infusion of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the two agents.

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m^2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter p<0.05). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity. Administration of cimetidine should be discontinued during treatment with epirubicin.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medications which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, antiretroviral agents).
The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area.

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

If epirubicin is used concomitantly with other drugs that may cause heart failure, e.g. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment.

Epirubicin is mainly metabolised in the liver; each concomitant medication which affects hepatic function can also affect the metabolisation or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity.

This product is generally not recommended in combination with live attenuated vaccines.

Pregnancy and lactation: There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should, if appropriate and available, seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy. Epirubicin may cause amenorrhea or premature menopause in premenopausal women.
Experimental data suggest that epirubicin may harm the foetus. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction and should use an effective method of contraception during treatment and for six month thereafter. Male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin. Women of childbearing potential should be fully informed of the potential hazard to the foetus and the possibility of genetic counseling should be considered if they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.
It is unknown whether epirubicin is excreted in human breast milk. A risk to the suckling child cannot be excluded Breastfeeding must be discontinued before and during therapy with Epirubicin.

Effects on ability to drive and use machines: There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines. Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

Undesirable effects: Adverse event frequencies have been categorised as follows:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common (≥1/10)	Blood and lymphatic system disorder	Myelosuppression (leucopenia, granulocytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anaemia). Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur. High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and has caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.
	Renal and urinary disorders	Chromaturie (urine red coloured)
	Skin and subcutaneous tissue disorders	Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
Common (≥ 1/100 to <1/10)	Gastrointestinal disorders	Nausea, vomiting, diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Oesophagitis and hyperpigmentation of the oral mucosa may also occur.
	Skin and subcutaneous tissue disorders	Hot flushes
	Injury, poisoning and procedural complications	Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration.
	General disorders and administration site conditions	Mucositis – may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa. Redness along the infusion vein. Local phlebitis, phlebosclerosis. Local pain and tissue necrosis (following accidental paravenous injection) may occur.
	Immune system disorders	Allergic reactions following intravesical administration.
	Metabolism and nutrition disorders	Anorexia, dehydration
Uncommon (≥1/1,1000 to <1/100)	Skin and subcutaneous tissue disorders	Hyperpigmentation of skin and nails. Skin reddening.
	Vascular disorders	Thrombophlebitis
	General disorders and administration site conditions	Headache
	Immune system disorders	Sensitivity to light or hypersensitivity in the case of radiotherapy ("recall phenomenon").
Rare (<1/10,000 to <1/1,000)	Investigations	Increased transaminase levels
	Cardiac disorders	Cardiotoxicity (ECG changes, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusions, gallop rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block (see section "**Special warnings and special precautions for use**").
	Skin and subcutaneous tissue	Urticaria
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Secondary acute myeloid leukaemia with or without a pre-leukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 year) latency.
	Immune system disorders	Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills)
	General disorders and administration site conditions	Fever, chills, dizziness, hyperuricaemia (as a result of rapid lysis of neoplastic cells). Hyperpyrexia, malaise, weakness have also been reported.
	Reproductive system and breast disorders	amenorrhea, azoospermia
	Infections and infestations	Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression.
Frequency Unknown	Vascular disorders	Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome]) have occurred.
	Eye disorders	Conjunctivitis, keratitis

Intravesical administration: As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria). Occasional bacterial or chemical cystitis have been reported (see section "**Special warnings and special precautions for use**"). These ADRs are mostly reversible.

Overdose: Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days. Treatment should aim to support the patient during this period and should utilise such measures as antibiotics, blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines. Epirubicin is not dialyzable.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties: Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03
Epirubicin is a cytotoxic active antibiotic from the anthracycline group.
The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

Pharmacokinetic properties: In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

In pharmacokinetic studies of patients with carcinoma in situ of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (<10 ng/ml). A significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumour, cystitis, operations), a higher resorption rate can be expected.
The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged drug.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The drug does not cross the blood brain barrier.

Preclinical safety data: Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.
Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.
No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.
A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

PHARMACEUTICAL PARTICULARS
List of excipients: Sodium Chloride, Hydrochloric Acid (for pH adjustment), Water for Injections.

Incompatibilities: This medicinal product must not be mixed with other medicinal products except those mentioned in section "**Instructions for use, handling and disposal**".

Shelf life: See expiry date (EXP) on the carton box and vial label. Do not use after the expiry date.

In-use shelf life: After first penetration of the stopper (and prior to dilution of the solution) – the Epirubicin Hydrochloride 2 mg/ml solution may be stored up to 24 hours at +2 to +8°C in the absence of light.

From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper and/or dilution. Any unused portion must be discarded after use. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be more than 12 hours at +25°C, unless penetration/dilution has taken place in controlled and validated aseptic conditions.

The Epirubicin Hydrochloride 2 mg/ml solution is compatible with dextrose 5% and sodium chloride 0.9%.
After dilution, the diluted drug has been shown to maintain its physiochemical stability in a Sodium Chloride Solution (0.9%) or a Glucose Solution (5%) for 12 hours at a maximum temperature of +25°C.
Nevertheless, from a microbiological point of view, the drug should be used immediately. If this is not the case, the user is exclusively responsible for the storage duration and conditions after the drug's dilution and before its utilization. The storage time should not exceed 12 hours at a maximum temperature of +25°C.

Special precautions for storage: Store in a refrigerator (+2°C to +8°C). Keep the vial in the outer carton in order to protect from light.

Nature and contents of container: EPIRUBICIN INOVAMED solution for injection is supplied in clear, type I borosilicate glass vials, for parenteral use, with chlorobutyl faced stoppers and aluminum seals with flip-off, containing various fill volumes (e.g., but not limited to: 5 ml, 10 ml, 25 ml, 50 ml or 100 ml of sterile solution of Epirubicin hydrochloride 2 mg/ml).

Not all pack sizes and presentations may be marketed. Other fill volumes and presentations might be available.

Instructions for use, handling and disposal: The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.
EPIRUBICIN INOVAMED solution for injection is compatible with dextrose 5% and sodium chloride 0.9%.

Guidelines for the safe handling and disposal of antineoplastic agents:
1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective disposable gloves, goggles, gown and mask should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
5. In case of skin contact, thoroughly was the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
6. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

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